NEW DEVELOPMENTS IN THE CHEMISTRY OF WAR GASES[1]

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I. Introduction

At the beginning of World War II, there were no chemical warfare agents of practical importance which were not known at the end of World War I. The various sources of information now available disclose that, in the event gas warfare had been initiated in 1940, the following chemical agents would have

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been used: phosgene, diphosgene, mustard gas, phenyldichloroarsine, diphenylchloroarsine, and adamsite (90).

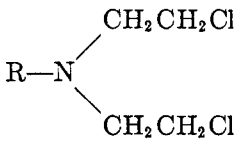
As the war spread, one of the first steps undertaken in every leading country was to set up broad programs of research with the purpose of finding new agents, more powerful than those already known. Over a period of about five years, many thousands of compounds were prepared and investigated to determine their toxicities and their potentialities as war gases. The large amount of work carried out on the preparation of these compounds led to the discovery of many interesting substances and to the development of several new methods of synthesis. In addition, the results of the toxicological investigations shed new light on the relation between chemical structure and toxicity and on the mechanism of the reaction of various compounds with living tissues.

The following three classes of compounds received special attention: (*1*) the nitrogen mustards, (*2*) the fluoroacetates, (*3*) the fluophosphates. The purpose of this article is to review briefly the history, preparation, and properties of these substances.

II. Nitrogen Mustards

A. Introduction

The "nitrogen mustards" are tertiary 2,2′-dihalodialkylamines, more particularly 2,2′-dichlorodiethylamines, of the structure



in which R is an alkyl, haloalkyl, or aryl group. The name "nitrogen mustards" is derived from the structural and toxicological similarity of these compounds to "mustard gas," 2,2′-dichlorodiethyl sulfide, $(ClCH_2CH_2)_2S$. They are also called "radiomimetic poisons," because many of their biological properties are like those of ionizing radiations (11).

The first member of this class of compounds to be prepared and described in regard to its vesicant action was the 2,2′,2″-trichlorotriethylamine (117). Several years later, during World War II, many representative compounds of this type were tested as war gases, the most important of which are listed in table 1. 2,2′,2″-Trichlorotriethylamine was thoroughly investigated, particularly by the Germans, who built industrial plants for its manufacture. At the end of hostilities 2000 metric tons of this compound was captured in Germany (116).

The tertiary 2,2′-dichlorodialkylamines are vesicants with toxic properties similar to those of "mustard gas." In addition, these amines in aqueous solution exhibit for a long time a neurotoxic action with a rapid lethal effect. Because of this toxicity their use as water contaminants was considered during World War II. Furthermore they are selective inhibitors of cholinesterase, but less potent in this respect than diisopropyl fluophosphate (1). It is believed that many of

the toxic effects of these amines are a consequence of their ability to form aziridinium ions, which react very rapidly with the functional groups of a number of substances essential to the economy of the living cell (10, 31).

Since the end of World War II, the tertiary 2,2′-dichlorodialkylamines have been intensively studied and physiological tests indicate that these compounds may have therapeutic applications (33, 38, 58).

The following correlations between chemical structure and toxicity may be made from the limited data reported in the literature: (*a*) The presence of two 2-haloalkyl groups appears to be essential for toxicity. (*b*) The increase in complexity of the molecule usually decreases the toxic characteristics. (*c*) In the *N*-aryl-2,2′-dichlorodiethylamines, a nuclear substituent which reduces the chemical reactivity of the halogen atoms causes a decrease in toxicity.

B. METHODS OF PREPARATION

The various methods for preparing these compounds are based upon the chlorination of the corresponding tertiary 2,2′-dihydroxydialkylamines in the presence or absence of a solvent. The most general and widely used chlorinating agent is thionyl chloride:

$$RN(CH_2CH_2OH)_2 + 2SOCl_2 \rightarrow RN(CH_2CH_2Cl)_2 + 2SO_2 + 2HCl$$

Phosphorus trichloride, according to Gorbovitskiĭ (39), gives fairly high yields of *N*-methyl-2,2′-dichlorodiethylamine. However, other investigators studying the influence of various chlorinating agents found that phosphorus trichloride, sulfuryl chloride, and sulfur monochloride gave lower yields of *N*-methyl-2,2′-dichlorodiethylamine than did thionyl chloride (50).

The procedure most frequently employed for preparing the *N*-alkyl-2,2′-dichlorodiethylamines involves the use of the hydrochlorides of *N*-alkyl-2,2′-dihydroxydiethylamines instead of the free amines. The reaction is carried out in boiling benzene (50, 56) or chloroform (27, 39) and in the presence of an excess of thionyl chloride. Yields varying from 75 to 84 per cent are reported.

Similar procedures can be used for preparing the 2,2′,2″-trihalotriethylamines (19, 71, 72, 117, 118). The trichloro compound was also obtained in the absence of a solvent, by heating 2,2′,2″-trihydroxytriethylamine hydrochloride with the calculated amount of thionyl chloride on a steam bath for 30 min. A 90–92 per cent yield of 2,2′,2″-trichlorotriethylamine of 99.5 per cent purity has been reported (22).

The *N*-aryl-2,2′-dichlorodiethylamines may be prepared, like the *N*-alkyl compounds, by chlorination of the corresponding 2,2′-dihydroxydiethylamines. In this case the best yields were obtained by using phosphoryl chloride. Phosphorus pentachloride and thionyl chloride gave lower yields (88).

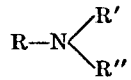
C. PROPERTIES AND REACTIONS

1. Physical properties

The tertiary 2,2′-dihalodialkylamines are colorless liquids when freshly distilled, having a very faint odor. The boiling points, densities, and refractive

TABLE 1

Tertiary 2,2′-dihalodialkylamines



NO.	R	R′	R″	BOILING POINT	$n_D^{25°}$	$d_{4°}^{25°}$	VAPOR PRESSURE CONSTANTS		HYDROCHLORIDE MELTING POINT	PICRATE MELTING POINT	REFERENCES
							A	*B*			
				°C.					°C.	°C.	
1.	CH_3	CH_2CH_2Cl	CH_2CH_2Cl	71/9 mm.					110	133	(50)
2.	C_2H_5	CH_2CH_2Cl	CH_2CH_2Cl	85.5/12 mm.	1.4653	1.0861[g]	9.01892	2868.9	141	100	(50, 87)
3.	*n*-C_3H_7	CH_2CH_2Cl	CH_2CH_2Cl	96/10 mm.	1.4629[a]	1.05929[g]	9.01884	2966.7		99	(50, 87)
4.	*i*-C_3H_7	CH_2CH_2Cl	CH_2CH_2Cl	90/8 mm.					216	75	(50)
5.	*n*-C_4H_9	CH_2CH_2Cl	CH_2CH_2Cl	106.3/9 mm.	1.4637	1.027[h]	9.28361	3169.8			(21, 87)
6.	*i*-C_4H_9	CH_2CH_2Cl	CH_2CH_2Cl	79/2 mm.	1.4597[a]	1.0328[i]	9.42242	3152.5			(21, 87)
7.	*sec*-C_4H_9	CH_2CH_2Cl	CH_2CH_2Cl	100/7.5 mm.	1.4655	1.0455	9.16684	3109.5			(21, 87)
8.	*tert*-C_4H_9	CH_2CH_2Cl	CH_2CH_2Cl	71–72/2 mm.	1.4710[b]	1.0484[j]	9.13430	3050.9			(21, 87)
9.	CH_3	CH_2CH_2Cl	$CH_2CH_2CH_2Cl$	104–106/23 mm.	1.4640[c]					75	(57)
10.	CH_3	CH_2CH_2Cl	$CH_2CHClCH_3$	94–94.5/21 mm.	1.4622[d]					122–123	(57)
11.	CH_3	CH_2CH_2Cl	$CH_2CH_2OCH_2CH_2Cl$						66	59	(50)
12.	CH_3	CH_2CH_2Cl	$COCH_2Cl$	110–112/0.8 mm.	1.5010[e]						(57)
13.	CH_3	$CH_2CHClCH_3$	$CH_2CHClCH_3$	82/9 mm.	1.4585[f]					110	(50)
14.	$CH{=}CHCH_3$	CH_2CH_2Cl	CH_2CH_2Cl	80/3 mm.							(28)
15.	CH_2CH_2Cl	CH_2CH_2Cl	CH_2CH_2Cl	94/1 mm.	1.4925	1.2093	9.41621	3393.4			(87)
16.	CH_2CH_2Cl	CH_2CH_2Cl	$CH_2CH_2CH_2Cl$	116/1.3 mm.	1.4936[d]					93–94	(57)
17.	CH_2CH_2Cl	$CH_2CHClCH_3$	$CH_2CHClCH_3$	117/3 mm.						117.5	(28)
18.	CH_2CH_2Br	CH_2CH_2Br	CH_2CH_2Br	145/0.05 mm.							(19)
19.	CH_3	CH_2CH_2F	CH_2CH_2F	123–124/762 mm.							(19)
20.	CH_2CH_2F	CH_2CH_2Cl	CH_2CH_2Cl	115/13 mm.							(19)
21.	CH_2CH_2Cl	CH_2CH_2F	CH_2CH_2F	95–97/19 mm.						121	(19)
22.	CH_2CH_2F	CH_2CH_2F	CH_2CH_2F	73–74/25 mm.							(19)

(a) $n_D^{27°}$. (b) $n_D^{20°}$. (c) $n_D^{22°}$. (d) $n_D^{17°}$. (e) $n_D^{18°}$. (f) $n_D^{19°}$. (g) $d_{4°}^{23°}$. (h) $d_{4°}^{26°}$. (i) $d_{4°}^{20°}$. (j) $d_{4°}^{22°}$.

indices are reported in table 1. The vapor pressures at different temperatures may be calculated by using the following formula (87):

$$\log p \text{ (mm.)} = A - B/T$$

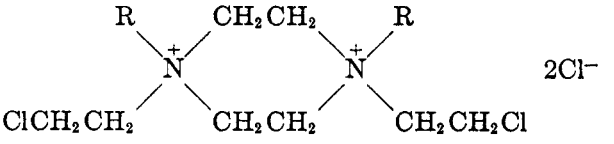
The values of the constants A and B are listed in table 1.

These amines are slightly soluble in water. The N-methyl-2,2′-dichlorodiethylamine is soluble to the extent of 1.2 per cent at room temperature (47). They are miscible with several organic solvents. The solutions in polar solvents are quite unstable; however, the solutions in dry acetone or ether can be kept for days without developing appreciable amounts of ionic chlorine (7).

Most of the N-aryl-2,2′-dichlorodiethylamines are light-sensitive and develop deep colors on exposure to air, especially in dilute solutions. Some exhibit a remarkably strong photoluminescence (88).

2. Dimerization

One of the first chemical properties of the tertiary-2,2′-dihalodialkylamines to be noticed is their tendency to polymerize. Pure N-alkyl-2,2′-dichlorodiethylamines and 2,2′,2″-trichlorotriethylamine on standing at room temperature over a period of time deposit a fluffy mass of small crystals, the rate of formation of which increases with an increase in temperature. Changes in the length of the alkyl chain R and the presence of solvents have also a large effect on the rate of the precipitation. These crystals were identified as dimers of the tertiary 2,2′-dichlorodiethylamines, having a piperazinium dichloride structure of the formula (50):



R = CH_3, C_2H_5, or CH_2CH_2Cl.

Two isomeric forms of the dimer were obtained, the *cis*-form predominating in the case of N-methyl-2,2′-dichlorodiethylamine.

Comparative studies of the rate of dimerization show that this rate falls off very markedly as the length of the alkyl chain R increases (50). 2,2′,2″-Trichlorotriethylamine dimerizes more slowly than N-methyl-2,2′-dichlorodiethylamine (26).

Polar solvents, particularly those containing hydroxyl groups, accelerate the dimerization. In methyl alcohol the dimerization of N-methyl-2,2′-dichlorodiethylamine is markedly exothermic and may proceed almost explosively, if the quantities of the materials involved are large (50). 2,2′,2″-Trichlorotriethylamine undergoes only a little dimerization in this solvent, the main reaction being a substitution resulting in 2,2′-dichloro-2″-methoxytriethylamine (26):

$$CH_3OCH_2CH_2N(CH_2CH_2Cl)_2$$

Nonionizing solvents, such as carbon tetrachloride, chloroform, dioxane, etc., act as stabilizing agents. Thiourea also appears to have possibilities as a stabilizer (114).

3. Hydrolysis

The reactions of the tertiary 2,2′-dichlorodiethylamines with water were the object of extensive research, especially since these compounds were considered as possible water contaminants.

(a) *N*-Alkyl-2,2′-dichlorodiethylamines in unbuffered water solution

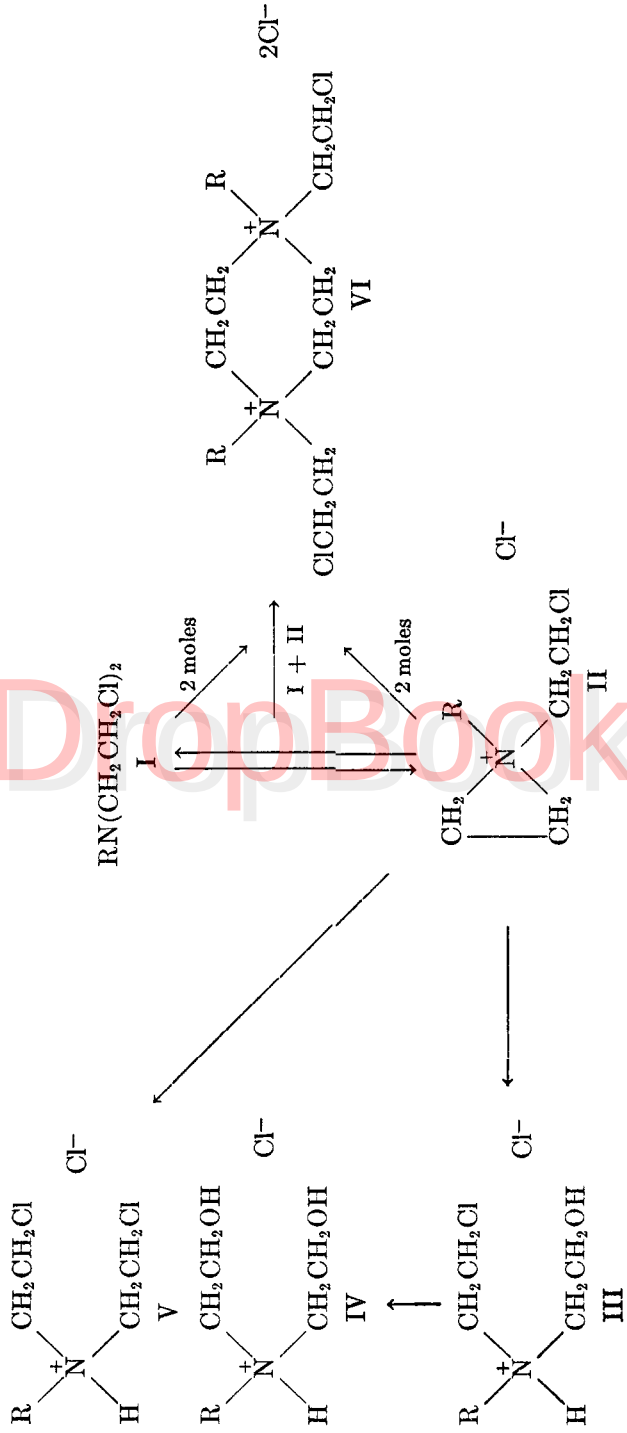
The various reactions which occur when an aqueous solution of an *N*-alkyl-2,2′-dichlorodiethylamine is kept at room temperature are summarized on page 231 (34, 47, 109).

The first reaction is a comparatively rapid cyclization of the amine (I) to 1-alkyl-1-(2-chloroethyl)aziridinium chloride (II). This aziridinium chloride is the main organic component of a 1 per cent solution of *N*-methyl-2,2′-dichlorodiethylamine which has been aged for 45 min. at 25°C. (47). As the hydrolysis proceeds, the aqueous solution undergoes further, comparatively slow, changes. The following reactions occur: (*i*) hydrolysis of II to 2-[(2-chloroethyl)alkylamino]ethanol hydrochloride (III) and *N*-alkyl-2,2′-dihydroxydiethylamine hydrochloride (IV); (*ii*) some reversion of II to the hydrochloride of the parent amine (V); and (*iii*) dimerization to the 1,4-dialkyl-1,4-bis(2-chloroethyl)piperazinium dichloride (VI).

The composition of a 1 per cent aqueous solution of *N*-methyl-2,2′-dichlorodiethylamine aged for 48 hr. at room temperature is 11 per cent of unchanged amine (I), 58 per cent of III, 2 per cent of IV, and 22 per cent of VI (35). After standing for a total of 70 hr. at room temperature, the amount of III decreases to 35 per cent, while the amount of IV increases to 20 per cent (49). 1,4-Dialkyl-1,4-bis(2-chloroethyl)piperazinium dichloride (VI) is the main stable quaternary ammonium salt present in the final equilibrium solution (50). It consists mostly of the *cis*-stereoisomer, but a much smaller amount of the *trans* compound is also present. The formation of this piperazinium dichloride probably takes place by interaction of two molecules of aziridinium chloride (II), although other mechanisms are not excluded (48).

Changes in length of the alkyl chain R have only a small effect on the degree of hydrolysis, but have a great effect on the amount of piperazinium dichloride (VI) produced, which decreases rapidly with increase in the length of R (49). The examples investigated are given in table 2.

In acetone–water solution *N*-methyl-2,2′-dichlorodiethylamine undergoes dimerization to 1,4-bis(2-chloroethyl)-1,4-dimethylpiperazinium dichloride with only a small amount (less than 10 per cent) of hydrolysis as a side reaction (8). The same types of products are formed in an acetone–water solution of 2,2′-dichlorotriethylamine. In this case, however, hydrolysis is the principal reaction and dimerization constitutes less than 50 per cent (7).


RN(CH2CH2Cl)2
I
2 moles
I + II
2 moles
2Cl−
ClCH2CH2
R
CH2CH2
CH2CH2Cl
VI
Cl−
CH2
CH2
CH2CH2Cl
II
Cl−
CH2CH2Cl
CH2CH2OH
III
Cl−
CH2CH2Cl
CH2CH2OH
IV
Cl−
CH2CH2Cl
CH2CH2Cl
V
H

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(b) *N*-Alkyl-2,2′-dichlorodiethylamines in aqueous bicarbonate solution (pH 8)

Unlike the reactions observed in unbuffered solution, *N*-methyl-2,2′-dichlorodiethylamine in aqueous bicarbonate solution (0.02 *M*) buffered at pH 8, aged for 72 hr. at 25°C., yields *N*-methyl-2,2′-dihydroxydiethylamine and 1,4-bis(2-hydroxyethyl)-1,4-dimethylpiperazinium dichloride. The 1,4-bis(2-chloroethyl)-1,4-dimethylpiperazinium dichloride is not formed appreciably in this case. The relative amounts of the hydrolytic end products vary depending upon the concentration of *N*-methyl-2,2′-dichlorodiethylamine in the solution (34). In very dilute solution the predominant reaction is hydrolysis to *N*-methyl-2,2′-dihydroxydiethylamine. As the concentration of *N*-methyl-2,2′-dichlorodiethylamine is raised, dimerization is favored and hydrolysis is reduced (20).

2,2′-Dichlorotriethylamine differs from its lower homolog in that the hydrolysis in aqueous bicarbonate solution proceeds almost exclusively to 2,2′-di-

TABLE 2

Composition of 1 per cent aqueous solutions of N-alkyl-2,2′-dichlorodiethylamines (I), aged for 70 hr. at 25°C. (49)

R	COMPOUNDS PRESENT IN THE SOLUTIONS (IN EQUIVALENTS PER CENT)				
	I + V	II	III	IV	VI
Methyl.....	20		35	20	25
Ethyl.....	28	5	35	28	4
n-Propyl.....	32	3	32	32	1
Isopropyl.....	30	2	37	30	1

hydroxytriethylamine. No dimeric salts were found among the products of the hydrolysis (29, 85).

(c) 2,2′,2″-Trichlorotriethylamine

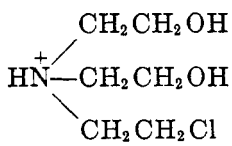
The hydrolysis of 2,2′,2″-trichlorotriethylamine in unbuffered water as a solvent proceeds very slowly at room temperature, especially after the formation of one equivalent of chloride ion. The release of this first equivalent requires about 20 hr. and some chloride ions are still liberated after 240 hr. (26).

The principal hydrolytic product of a solution aged for 20 hr. at room temperature is 2-[bis(2-chloroethyl)amino]ethanol hydrochloride (VII) (22, 37):

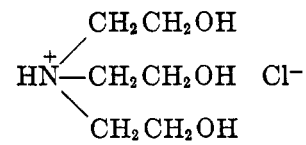
$$[HOCH_2CH_2\overset{+}{N}H(CH_2CH_2Cl)_2]Cl^-$$

VII

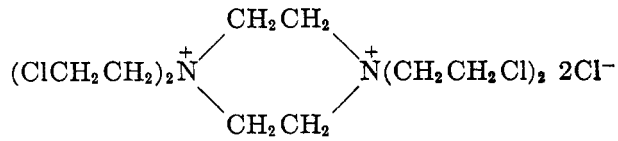
From a solution aged for 72 hr. at 25°C., 2,2′-(2-chloroethylimino)diethanol hydrochloride (VIII), 2,2′,2″-trihydroxytriethylamine hydrochloride (IX), and a small amount (about 4 per cent) of 1,1,4,4-tetrakis(2-chloroethyl)piperazinium dichloride (X) were isolated (26).



VIII

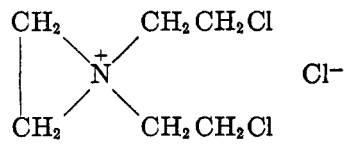


IX



X

In acetone–water solution 2,2′,2″-trichlorotriethylamine is hydrolyzed slowly to VII, with 10 per cent or less accumulation of 1,1-bis(2-chloroethyl)aziridinium chloride (XI) as an intermediate (9):



XI

The hydrolysis of 2,2′,2″-trichlorotriethylamine in sodium bicarbonate solution at pH 8 proceeds through successive stages to 2,2′,2″-trihydroxytriethylamine. The release of the first equivalent of chloride ion is in this case fairly rapid (within about 15 min.). The other two equivalents are formed much more slowly, chloride ions being still liberated after 4 hr. However, almost complete hydrolysis (90–95 per cent) is attained in less than 24 hr. Quaternary nitrogen compounds, largely present in the form of aziridinium ions, are formed during the first 15 min. As the reaction continues the amount of these compounds remains fairly constant for some time and then decreases, and after 24 hr. they are practically no longer present in the reaction mixture (37).

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4. Chlorination

The reactions of the *N*-alkyl-2,2′-dichlorodiethylamines with chlorinating agents result in dealkylation, due mainly to chlorination of the alkyl group.

When an *N*-alkyl-2,2′-dichlorodiethylamine is treated with chlorine in carbon tetrachloride solution, at least half of the base is precipitated as the hydrochloride, the remainder being chlorinated in the alkyl group. Aldehydes and 2,2′-dichlorodiethylamine have been identified among the products of the reaction, after treatment of the carbon tetrachloride solution with water.

$$CH_3N(CH_2CH_2Cl)_2 + Cl_2 \rightarrow ClCH_2N(CH_2CH_2Cl)_2 + HCl$$

$$ClCH_2N(CH_2CH_2Cl)_2 + H_2O \rightarrow HN(CH_2CH_2Cl)_2 + HCHO + HCl$$

Simultaneously there is some attack on the 2-chloroethyl group, in both the 1- and the 2-positions, since chloral, glyoxal, and *N*-alkyl-2-chloroethylamine have also been isolated (25).

The action of aqueous chlorinating agents, such as sodium or calcium hypochlorite, on the tertiary 2,2′-dichlorodiethylamines is similar to but somewhat more complicated than that of anhydrous chlorinating agents. When a tertiary 2,2′-dichlorodiethylamine hydrochloride is added to a sodium hypochlorite solution at pH 8 and buffered with sodium bicarbonate, several products are formed, among which *N*-2,2′-trichlorodiethylamine was identified (25, 85).

$$RN(CH_2CH_2Cl)_2 \xrightarrow[pH\ 8]{OCl^-} ClN(CH_2CH_2Cl)_2$$

R = CH_3, C_2H_5, or CH_2CH_2Cl.

The *N*-2,2′-trichlorodiethylamine when treated with hydrochloric acid gives 2,2′-dichlorodiethylamine, as shown in the reaction:

$$ClN(CH_2CH_2Cl)_2 \xrightarrow{HCl} HN(CH_2CH_2Cl)_2 + Cl_2$$

Chloramine-T, used as a decontaminating agent in chemical warfare, does not react with 2,2′,2″-trichlorotriethylamine at room temperature in the presence of sodium bicarbonate (85). The tertiary 2,2′-dichlorodiethylamines inflame when treated in bulk with dry bleaching powder. This is the most rapid way of effecting their destruction.

5. Miscellaneous reactions

The tertiary 2,2′-dihalodialkylamines form salts with mineral acids and yield well-defined crystalline derivatives with picric acid. The melting points of these derivatives are reported in table 1. The hydrochlorides are very stable compounds and in many instances they provide a convenient form for storing these amines.

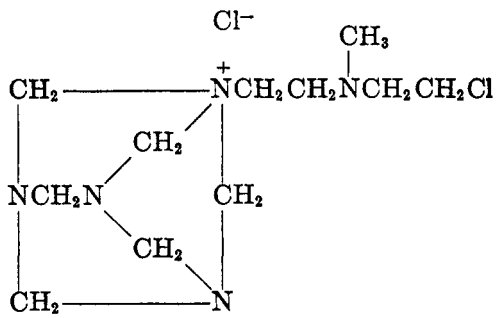
(a) With amines

Aniline reacts with *N*-methyl-2,2′-dichlorodiethylamine hydrochloride in boiling methyl alcohol to give 1-methyl-4-phenylpiperazine (82). By refluxing a mixture of two moles of aniline with one mole of 2,2′,2″-trichlorotriethylamine hydrochloride, 1-(2-anilinoethyl)-4-phenylpiperazine is obtained (2):

$$2C_6H_5NH_2 + N(CH_2CH_2Cl)_3 \longrightarrow C_6H_5NHCH_2CH_2N\begin{array}{l}\diagup CH_2CH_2 \diagdown \\ \\ \diagdown CH_2CH_2 \diagup\end{array}NC_6H_5$$

When equimolar amounts of *N*-methyl-2,2′-dichlorodiethylamine and hexamethylenetetramine are mixed and allowed to stand in 50 per cent aqueous ethyl alcohol for 30 min. at room temperature, a variety of products is formed,

among which the hexamethylenetetraminium derivative of *N*-methyl-2,2′-dichlorodiethylamine was isolated (36, 46):



The 2-chloroethyl groups of the tertiary 2,2′-dichlorodiethylamines show practically equal reactivity toward the amino groups of amino acids and of peptides. 2,2′,2″-Trichlorotriethylamine seems to have a greater reactivity toward the β-amino group of β-alanine and toward the sulfide group of methionine than does *N*-methyl-2,2′-dichlorodiethylamine or 2,2′-dichlorotriethylamine. On the other hand, *N*-methyl-2,2′-dichlorodiethylamine seems to have the highest reactivity toward the imidazole group of histidine (30).

The *N*-aryl-2,2′-dichlorodiethylamines also react with primary amines to form 1,4-disubstituted piperazines. The yields of this reaction vary between 40 and 70 per cent, being higher with the more basic amines (89).

DropBooks

(b) With peracids

Tertiary 2,2′-dichlorodiethylamines when treated in aqueous solution with peracids, such as peracetic acid, are oxidized to the corresponding *N*-oxides:

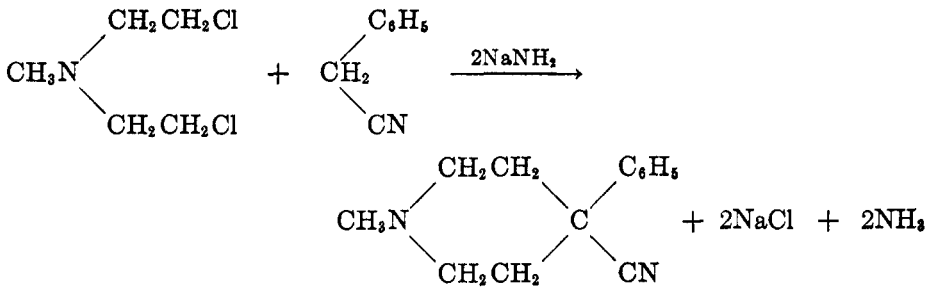
$$RN(CH_2CH_2Cl)_2 \longrightarrow RN(CH_2CH_2Cl)_2 \downarrow O$$

R = CH_3, C_2H_5, or CH_2CH_2Cl.

This oxidation is rapid in weakly alkaline solution and slow in acid solution. The amine oxides are isolated as hydrochlorides in 78–85 per cent yields (110). These high yields indicate that oxidation of the nitrogen atom proceeds more rapidly than does hydrolysis of the 2-chloroethyl group. The amine *N*-oxides still possess appreciable toxicity (110).

(c) With benzyl cyanide

N-Methyl-2,2′-dichlorodiethylamine condenses with benzyl cyanide in the presence of sodium amide to form 1-methyl-4-phenylisonipecotonitrile, in 66 per cent yield:



This nitrile, by saponification, gives 1-methyl-4-phenylisonipecotic acid, from which 1-methyl-4-phenyl-piperidine is obtained by decarboxylation (27).

III. Fluoroacetates

A. Introduction

The class of compounds known as "fluoroacetates" comprises the esters of fluoroacetic acid and of higher ω-fluorocarboxylic acids, of the general formula:

$$F(CH_2)_nCOOR$$

Various other fluorine compounds, such as ω-fluoroalcohols, α-fluoroacetamide, and their derivatives are generally included in this class. They are collectively named "fluoroacetates" because their toxic properties are similar to those of methyl fluoroacetate.

The discovery of this class of substances was reported in 1896 by Swarts, who prepared methyl fluoroacetate (112). Over the next forty years several "fluoroacetates" were described, but it was not until the high toxicity of 2-fluoroethanol and of fluoroacetic acid was recognized in 1936 that systematic study resulted (43).

The first compound investigated for possible chemical warfare use was methyl fluoroacetate. Many other "fluoroacetates" were prepared and tested for their toxicities, particularly in Poland (44) and in England (74). The most important are listed in tables 3 to 7, inclusive. During World War II, it was planned to use these compounds especially as water contaminants, because of their stability in water solution and their lack of taste or odor.

The "fluoroacetates" are highly toxic when inhaled, injected, and to some extent when absorbed through the skin. They act as convulsant poisons with a delayed effect. Unlike the other haloacetates they do not possess lachrymatory properties, and unlike the fluophosphates they are completely devoid of myotic activity.

From the data available it is possible to formulate the following correlations between chemical structure and toxicity of the "fluoroacetates" (*cf.* tables 3 to 7, inclusive):

(a) Compounds able to form the FCH_2CO— radical either by oxidation or by hydrolysis are toxic. Any substitution in this radical decreases or destroys the toxicity.

(b) Esters of the type $F(CH_2)_nCOOC_2H_5$ are toxic when n is an odd number, whereas they are practically devoid of any toxicity when n is an even number. This alternate toxicity is explained in the light of the β-oxidation theory of the long-chain fatty acids in the animal body (62). Thus, according to Saunders (14, 81, 91), when n is odd, β-oxidation will give the toxic fluoroacetic acid, whereas when n is even, the compound will be oxidized only as far as the nontoxic β-fluoropropionic acid, which is unable to give fluoroacetic acid by the process of β-oxidation.

(c) An increase in n of the above esters causes a gradual increase in toxicity, reaching a maximum when n is 5, beyond which the toxicity decreases.

(d) In esters of this type, when n is odd and less than 9, the toxicity increases if the ethyl group is replaced by a 2-fluoroethyl group.

B. UNSUBSTITUTED ESTERS OF ω-FLUOROCARBOXYLIC ACIDS

1. Methods of preparation

Swarts obtained methyl fluoroacetate by reacting methyl iodoacetate with silver or mercurous fluoride (112):

$$ICH_2COOCH_3 + AgF \rightarrow FCH_2COOCH_3 + AgI$$

In order to adapt this method to large-scale production, other less expensive haloacetates and a variety of fluorinating agents were investigated during World War II. A method of wide application was developed by Gryszkiewicz-Trochimowski (44) and by McCombie (74). It consists, in the case of methyl fluoroacetate, in heating at 190–200°C. for 10–15 hr. methyl chloroacetate with an excess of potassium fluoride in an autoclave. Yields of 60 per cent (93) and 90 per cent (44) are reported. Sodium fluoride under the same conditions gave very poor yields.

$$ClCH_2COOCH_3 + KF \rightarrow FCH_2COOCH_3 + KCl$$

Several other fluoroacetates have been prepared by using this method. The yields varied from 20 to 90 per cent. The best conditions for the reaction are: (*a*) complete dryness of the starting materials, (*b*) large excess of potassium fluoride, 10 to 50 per cent, (*c*) strong agitation, and (*d*) high temperatures (44). This method was used in the United States for the preparation of methyl fluoroacetate on a pilot-plant scale (4).

Other methods for preparing alkyl fluoroacetates are based upon the following reactions:

(a) Reaction of alkyl bromoacetate with anhydrous thallous fluoride. By means of this reaction, only the methyl and ethyl fluoroacetates could be prepared (86).

(b) Reaction of ethyl diazoacetate with hydrofluoric acid.

$$N_2CHCOOC_2H_5 + HF \rightarrow FCH_2COOC_2H_5 + N_2$$

According to Schrader, this reaction furnishes a good laboratory procedure for preparing ethyl fluoroacetate (101).

DropBooks

(c) Condensation of ethyl alcohol with fluoroacetyl fluoride obtained by vapor-phase fluorination of acetyl fluoride with fluorine. The yields were poor and the resulting ethyl fluoroacetate was contaminated with ethyl difluoroacetate (79).

(d) Ester interchange between ethyl fluoroacetate and an alcohol, such as 2-ethyl-1-hexanol or dodecyl alcohol, in the presence of *p*-toluenesulfonic acid as the catalyst. Yields varying from 60 to 80 per cent were obtained (6, 54).

The following methods were used for preparing higher ω-fluorocarboxylic acids, and their esters:

(a) Oxidation of the corresponding ω-fluoroalcohols with potassium dichromate and sulfuric acid, followed by esterification of the carboxylic acid obtained. The yields of the oxidation step were 75–80 per cent (42).

(b) Reaction of the esters of ω-bromo- or ω-iodocarboxylic acids with dry silver fluoride at room temperature or at 50–80°C., in the absence of a solvent (14). The yields varied from 12 to 27 per cent of the theoretical.

2. Properties and reactions

The unsubstituted alkyl esters of ω-fluorocarboxylic acids are generally colorless stable liquids of very faint fruit-like odors. Methyl fluoroacetate is practically odorless, concentrations of one part per million being undetectable, and it is completely miscible with most of the organic solvents as well as with mustard gas (2,2′-dichlorodiethyl sulfide). The solubility in water is about 15 per cent (93). In tables 3 and 4 are listed other properties of these esters.

The hydrolysis of methyl fluoroacetate according to the equation

$$FCH_2COOCH_3 + H_2O \rightarrow FCH_2COOH + CH_3OH$$

is very slow, only 2.5 per cent of methyl fluoroacetate being hydrolyzed at room temperature within 60 hr. This hydrolysis is catalyzed by alkali to a much greater degree than by acid (84). The fluorine atom is remarkably inert. No free fluoride ion is formed when methyl fluoroacetate is refluxed with 20 per cent alcoholic potassium hydroxide for 5 min. After 20 hr. of refluxing, a 50 per cent conversion into potassium fluoride is obtained (93). When methyl fluoroacetate is heated at 88°C. with an excess of sodium thiosulfate, fluorine is displaced to the extent of 30 per cent in 8 hr. (84).

Dilute aqueous solutions of sodium hypochlorite do not decompose methyl fluoroacetate. Vigorous oxidizing agents, such as chromic acid and sulfuric acid, cause complete decomposition of this ester to carbon dioxide, hydrogen fluoride, and water (83).

Treatment of an aqueous solution of methyl fluoroacetate with an excess of calcium hydroxide (45) or barium hydroxide (93) and evaporation under vacuum yields a crystalline residue of calcium or barium fluoroacetate. This salt, mixed with sulfuric acid and distilled under reduced pressure, gives a 90 per cent yield of fluoroacetic acid.

When an excess of aqueous ammonia is added to methyl fluoroacetate, cooled in ice water, a crystalline precipitate of α-fluoroacetamide is obtained in quanti-

tative yield. It is a stable compound and it has proved to be of great value as an analytical standard for organic fluorine compounds (17). This amide is as

TABLE 3

Esters of fluoroacetic acid, FCH_2COOR

NO.	R	BOILING POINT*	PREPARATIVE PROCEDURE†	YIELD	TOXICITY COMPARED WITH METHYL FLUOROACETATE‡	REFERENCES
		°C.		*per cent*		
1...	CH_3	104.5–105	A	90	Standard	(44, 93)
2...	C_2H_5	117–121	A	75	Similar	(44, 93)
3...	n-C_3H_7	135–137	A		Similar	(93)
4...	i-C_3H_7	124	A	42	Similar	(93)
5...	$C_4H_9(C_2H_5)CHCH_2$	65–68/2 mm.	B	79.5		(6)
6...	$C_{12}H_{25}$	106–128/1 mm.	B	59		(6)
7...	C_6H_5	§	C	100	Similar	(93)

* Pressures not indicated are atmospheric.

† A: by reacting the corresponding ester of chloroacetic acid with potassium fluoride.
B: by reacting the corresponding alcohol with ethyl fluoroacetate.
C: by reacting phenol with fluoroacetyl chloride.

‡ Toxicity of methyl fluoroacetate: $L.C._{50}$ = 0.1 mg./l. for rabbits, guinea pigs, and rats ($L.C._{50}$ is the concentration in milligrams per liter required to kill 50 per cent of the animals exposed for 10 min.) (93).

§ Melting point, 63.5–64°C.

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TABLE 4

Ethyl esters of ω-fluorocarboxylic acids, $F(CH_2)_nCOOC_2H_5$

NO.	n	BOILING POINT	PREPARATIVE PROCEDURE*	YIELD	TOXICITY $L.D._{50}$†	REFERENCES
		°C.		*per cent*	*mg./kg.*	
1.....	1	117–121/760 mm.	A	75	~15	(44, 93, 94)
2.....	2				Nontoxic	‡
3.....	3				Toxic	‡
4.....	4	56–60/16 mm.	B		>160	(14)
5.....	5	82–84/14 mm.	B	27	4	(14)
6.....	7	145–150/12 mm.	B		9	(14)
7.....	9	135–138/10 mm.	B	20	10	(14)
8.....	10	140–141/11 mm.	B	19	>100	(14)
9.....	11	152–153/11 mm.	B	12	<20	(14)

* A: by reacting ethyl chloroacetate with potassium fluoride.
B: by reacting the corresponding ethyl ω-bromo- or ω-iodocarboxylate with silver fluoride.

† Dose in milligrams per kilogram of body weight to kill 50 per cent of the mice treated by subcutaneous injection of propylene glycol solutions. $L.D._{50}$ of methyl fluoroacetate = 15 mg./kg. (14). Compounds having an $L.D._{50}$ value greater than 100 are considered to be nontoxic.

‡ Private communication regarding work done in the United States; *cf.* reference 91.

toxic as methyl fluoroacetate (13). Treatment of α-fluoroacetamide with phosphorus pentoxide, at 110–115°C. and atmospheric pressure, yields fluoroacet-

onitrile as a colorless mobile liquid, less toxic than methyl fluoroacetate (13). When an aqueous solution of methylamine is added to methyl fluoroacetate, α-fluoro-*N*-methylacetamide, in 75 per cent yield, is produced (13).

C. 2-FLUOROETHYL ESTERS OF ω-FLUOROCARBOXYLIC ACID

1. Methods of preparation

2-Fluoroethyl fluoroacetate was prepared in 1943, with the hope of obtaining a compound having the combined toxicity of fluoroacetic acid and 2-fluoroethanol. A 77.4 per cent yield of this fluoroacetate was obtained by refluxing for 30 min. a mixture of fluoroacetyl chloride with 2-fluoroethanol (94):

$$FCH_2COCl + FCH_2CH_2OH \rightarrow FCH_2COOCH_2CH_2F + HCl$$

This ester was also prepared by direct fluorination of 2-chloroethyl chloroacetate with 30 per cent excess of potassium fluoride under pressure at 220°C. for 15 hr. (44). The yields were low (less than 14 per cent) and the product was always contaminated with the chloro ester (94). Recently another method has been reported for preparing 2-fluoroethyl fluoroacetate. It consists in heating a mixture of 2-fluoroethyl iodoacetate, mercuric fluoride, and potassium fluoride at 135°C. for 5 hr. The yields were also poor,—24.5 per cent (69).

The 2-fluoroethyl esters of higher ω-fluorocarboxylic acids were prepared by heating for a short time at 40–70°C. the 2-fluoroethyl esters of ω-bromo- or ω-iodocarboxylic acids with silver fluoride in the absence of solvents (14). The yields varied from 17 to 21 per cent of the theoretical.

2. Properties

2-Fluoroethyl fluoroacetate is a colorless liquid of very faint odor. The vapor pressures at 0°, 15°, and 30°C. are respectively 0.45, 1.28, and 3.29 mm. The toxicity of this ester in comparison with that of other related compounds is reported in table 5 (94). The 2-fluoroethyl esters of higher ω-fluorocarboxylic acids are colorless mobile liquids with a pleasant fruit-like odor and fairly high boiling points (*cf.* table 5). The results of the toxicological tests reported in table 5, compared with those in table 4, show that the 2-fluoroethyl esters are more toxic than the corresponding unsubstituted ethyl esters. This difference in toxicity is greater the shorter the carboxylic acid chain. With the η-fluorocaprylates this difference is slight and it becomes negligible with the ι-fluorocaprates. 2-Fluoroethyl ϵ-fluorocaproate is the most toxic compound of this series. It is eleven times as toxic as methyl fluoroacetate (mole for mole) (14).

D. ω-FLUOROALCOHOLS

1. Methods of preparation

Swarts (113) prepared 2-fluoroethanol in 1914, by the indirect method of hydrolyzing 2-fluoroethyl acetate with dilute mineral acids:

$$CH_3COOCH_2CH_2F \xrightarrow{H_2SO_4} FCH_2CH_2OH + CH_3COOH$$

This method was later improved by Gryszkiewicz-Trochimowski and was also used for preparing higher ω-fluoroalcohols. Yields varying from 75 to 85 per cent are reported (41).

A simpler method of synthesis was developed in 1943. It consists in heating ethylene chlorohydrin and potassium fluoride at 135°C. for 4 hr. in a rotating autoclave.

$$ClCH_2CH_2OH + KF \rightarrow FCH_2CH_2OH + KCl$$

The yield was 42 per cent. Sodium fluoride under the same conditions gave very poor yields (96). This reaction can also be carried out at atmospheric pressure, by using high-boiling organic solvents, such as ethylene glycol, glycerol, di-

TABLE 5

2-Fluoroethyl esters of ω-fluorocarboxylic acids and related compounds, $RCOOCH_2CH_2F$

NO.	R	BOILING POINT	PREPARATIVE PROCEDURE*	YIELD	TOXICITY L.D.$_{50}$†	REFERENCES
		°C.		*per cent*	*mg./kg.*	
1.....	CH_3	118–119/760 mm.	A	Theoretical	>15	(94)
2.....	$ClCH_2$	178/760 mm.	A	92.8	<15	(94)
3.....	FCH_2	158/760 mm.	A	77.4	8.5	(14, 94)
4.....	$F(CH_2)_5$	103–105/14 mm.	B		2.5	(14)
5.....	$F(CH_2)_7$	128–130/13 mm.	B	21	7	(14)
6.....	$F(CH_2)_9$	145–149/12 mm.	B	17	10	(14)

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* A: by reacting 2-fluoroethanol with acetyl chloride or with the corresponding haloacetyl chloride.

B: by reacting the corresponding 2-fluoroethyl ω-bromo- or ω-iodocarboxylate with silver fluoride.

† Dose in milligrams per kilogram of body weight to kill 50 per cent of the mice treated by subcutaneous injection of propylene glycol solutions. L.D.$_{50}$ of methyl fluoroacetate = 15 mg./kg. (14).

ethylene glycol, or polyethylene glycol, either singly or in admixture. A 42.5 per cent yield of 2-fluoroethanol was obtained by reacting ethylene chlorohydrin with potassium fluoride at 170–180°C. in a mixture of ethylene glycol and diethylene glycol (53).

Other methods of preparation are based upon the following reactions:

(a) Pyrolysis at 150–170°C. of tetrakis(2-hydroxyethyl)ammonium fluoride, obtained from the corresponding hydroxide and aqueous hydrofluoric acid (98):

$$(HOCH_2CH_2)_4NOH + HF \rightarrow (HOCH_2CH_2)_4NF + H_2O$$

$$(HOCH_2CH_2)_4NF \rightarrow HOCH_2CH_2F + (HOCH_2CH_2)_3N$$

(b) Reaction of ethylene glycol monosodium sulfate with sodium fluoride at 250–300°C. (97).

$$HOCH_2CH_2OSO_2ONa + NaF \rightarrow FCH_2CH_2OH + Na_2SO_4$$

(c) Condensation of ethylene oxide with anhydrous hydrogen fluoride in ethyl ether at 100°C. for 6 hr. This reaction gave a mixture of fluorinated products, from which 2-fluoroethanol was isolated in 40 per cent yield (63).

Following a technique similar to that above described for preparing 2-fluoroethanol from ethylene chlorohydrin, 3-fluoro-1-propanol was obtained in 40 per cent yield, by heating 3-chloro-1-propanol and potassium fluoride at 155–170°C. for 4 hr. in a rotating autoclave (15).

2. Properties and reactions of 2-fluoroethanol

2-Fluoroethanol is a colorless liquid of very faint odor, resembling that of ethyl alcohol. The vapor pressures at 0°, 15°, and 30°C. are respectively 5.55, 14.3, and 40 mm. (96). It is miscible with water in all proportions and readily dissolves calcium chloride and calcium nitrate (113).

2-Fluoroethanol is more resistant than ethyl alcohol toward oxidizing agents. By warming it with potassium dichromate and sulfuric acid, fluoroacetaldehyde is formed in very poor yields. Better yields are obtained by using manganese dioxide and sulfuric acid (96). The oxidation with alkaline potassium permanganate gives small amounts of fluoroacetic acid (69).

When thionyl chloride is added to 2-fluoroethanol in equimolar quantity and the mixture is heated in an oil bath at 90°C. for 30 min., 1-chloro-2-fluoroethane, $ClCH_2CH_2F$, is produced in 44 per cent yield. The chlorine atom of this compound is very unreactive toward a variety of reagents (96). According to Schrader, treatment of 2-fluoroethanol with thionyl chloride yields 2,2′-difluorodiethyl sulfite, $(FCH_2CH_2O)_2SO$, a compound having an insecticidal action similar to that of nicotine (99).

When 2-fluoroethanol is added to an excess of sulfuryl chloride and the mixture is warmed at 60°C., a 62 per cent yield of 2-fluoroethyl chlorosulfonate, $FCH_2CH_2OSO_2Cl$, is obtained (67), whereas 2,2′-difluorodiethyl sulfate, $(FCH_2CH_2O)_2SO_2$, is formed when sulfuryl chloride is added to slightly more than the theoretical quantity of 2-fluoroethanol (96). 2-Fluoroethyl chlorosulfonate exhibits a toxicity similar to that of methyl fluoroacetate. On the other hand, 2,2′-difluorodiethyl sulfate is less toxic and is nonirritating (96). The latter is a useful fluoroethylating agent (74).

2-Fluoroethanol reacts with phosphorus trichloride, in the presence of pyridine, giving an unstated yield of tris(2-fluoroethyl) phosphite, $(FCH_2CH_2O)_3P$, a liquid acting as a depressant on the central nervous system (66). Treatment of 2-fluoroethanol with phosgene at 0–2°C. gives an 81 per cent yield of 2-fluoroethyl chlorocarbonate, FCH_2CH_2OCOCl, whose vapors irritate the mucous membranes (68).

2-Fluoroethanol gives solid derivatives with α-naphthyl isocyanate and with 3,5-dinitrobenzoyl chloride (96). When a mixture of 2-fluoroethanol and ethylene oxide is heated at 130°C. for 4 hr., in the presence of anhydrous sodium sulfate as a catalyst, 2-(2-fluoroethoxy)ethanol, $FCH_2CH_2OCH_2CH_2OH$, is formed in 70 per cent yield (15).

2-Fluoroethanol when stirred with acrylonitrile and aqueous potassium hydroxide at room temperature for 17 hr. gives a 64 per cent yield of β-(2-fluoroethoxy)propionitrile, $FCH_2CH_2OCH_2CH_2CN$, which by hydrolysis with concentrated hydrochloric acid yields β-(2-fluoroethoxy)propionic acid, $FCH_2CH_2OCH_2CH_2COOH$. The toxicity of the nitrile is similar to that of 2-fluoroethanol, whereas the toxicity of the acid is considerably less (15).

3. Properties and reactions of higher ω-fluoroalcohols

The higher homologs of 2-fluoroethanol are colorless liquids of characteristic odor. They are soluble in water and in a majority of organic solvents, but only slightly soluble in petroleum ether (41). Other properties of these alcohols are listed in table 6.

TABLE 6

ω-Fluoroalcohols, $F(CH_2)_nOH$

NO.	n	BOILING POINT*	REACTANTS	YIELD	TOXICITY	REFERENCES
		°C.		*per cent*		
1..	2	103.5	$ClCH_2CH_2OH + KF$	42	Similar to methyl fluoroacetate	(96)
		100–102	$CH_3COOCH_2CH_2F + H_2O$ (H_2SO_4)	75		(41)
2..	3	123–128	$ClCH_2CH_2CH_2OH + KF$	40	Nontoxic	(15)
		127.5–128	$CH_3COOCH_2CH_2CH_2F + H_2O$ (H_2SO_4)	80		(41)
3..	4	52–53/11 mm.	$CH_3COOCH_2CH_2CH_2CH_2F + H_2O$ (H_2SO_4)	85		(41)

* Pressures not indicated are atmospheric.

When a solution of potassium dichromate in dilute sulfuric acid is added to 3-fluoro-1-propanol, β-fluoropropionic acid is obtained in 80 per cent yield (42). Treatment of 3-fluoro-1-propanol with acrylonitrile and aqueous potassium hydroxide at a temperature below 60°C. gives a 76 per cent yield of β-(3-fluoropropoxy)propionitrile, $F(CH_2)_3O(CH_2)_2CN$, a colorless liquid insoluble in water. By heating this compound with hydrochloric acid for 4 hr. on a boiling water bath, β-(3-fluoropropoxy)propionic acid, $F(CH_2)_3O(CH_2)_2COOH$, is formed in 32 per cent yield, as a colorless, water-soluble liquid. Like 3-fluoro-1-propanol this acid is nontoxic (15).

4-Fluoro-1-butanol heated with 40 per cent hydrobromic acid in a sealed tube at 120°C. gives 1,4-dibromobutane (41). Addition of a solution of potassium dichromate in dilute sulfuric acid to 4-fluoro-1-butanol gives a 75 per cent yield of γ-fluorobutyric acid. It is a colorless oil, soluble in water and in most of the

TABLE 7

Various "fluoroacetates"

NO.	FORMULA	BOILING POINT*	REACTANTS	YIELD	TOXICITY COMPARED WITH METHYL FLUOROACETATE	REFERENCES
		°C.		*per cent*		
1.	$ClCH_2COF$	73–76	$ClCH_2COCl + KF$	55.6	Nontoxic	(93)
2.	FCH_2COCl	71.5–73	$FCH_2COOH + PCl_5$		Similar	(45, 93)
3.	FCH_2COF	50.5–51	$FCH_2COCl + SbF_3$	64.4	Similar	(45, 93)
4.	FCH_2CONH_2	†	$ClCH_2CONH_2 + KF$	50		(5, 6, 12, 112)
			$FCH_2COOCH_3 + NH_3$	100	Similar	(13, 74)
5.	FCH_2CN	80	$FCH_2CONH_2 + P_2O_5$	65	Less toxic	(13)
6.	$FCH_2CONHCH_3$	‡	$FCH_2COOCH_3 + CH_3NH_2$	75		(13)
7.	$FCH_2CONHCH_2CH_2Cl$	§	$FCH_2CONHCH_2CH_2OH + SOCl_2$	87	Similar; nonvesicant	(13)
8.	$FCH_2CON(CH_2CH_2Cl)_2$	102/0.04 mm.	$FCH_2CON(CH_2CH_2OH)_2 + SOCl_2$		Similar; nonvesicant	(13)
9.	FCH_2CHO		$FCH_2CH_2OH + H_2SO_4 + MnO_2$		Similar	(96)
10.	$(FCH_2CH_2O)_2CH_2$	162–164	$FCH_2CH_2OH + (CH_2O)_3 + HCl$	50		(65, 100)
11.	$FCH_2CH_2OCH_2CH_2OH$	81/22 mm.	$FCH_2CH_2OH + CH_2OCH_2$	70		(15, 97)
12.	$FCH_2CH_2OCH_2CH_2CN$	104/15 mm.	$FCH_2CH_2OH + CH_2{=}CHCN$	64	Similar	(15)
13.	FCH_2CH_2OCOCl	129–131	$FCH_2CH_2OH + COCl_2$	81	Irritant	(68)
14.	$FCH_2CH_2OCOCH_2Cl$	83–85/15 mm.	$FCH_2CH_2OH + ClCH_2COCl$	30	Irritant	(69)
15.	$FCH_2CH_2OSO_2Cl$	80/18 mm.	FCH_2CH_2OH to SO_2Cl_2 (excess)	62	Similar; irritant	(67, 96)
16.	$(FCH_2CH_2O)_2SO_2$	145/18 mm.	$SO_2Cl_2 + FCH_2CH_2OH$		Less toxic, nonirritant	(67, 96)
17.	$(FCH_2CH_2O)_3P$	114–116/8 mm.	$FCH_2CH_2OH + PCl_3$		Depressant of the central nervous system	(66)
18.	$(FCH_2CH_2O)_3PO$	169/11 mm.	$POCl_3$ to FCH_2CH_2OH	60		(67)
19.	$FCH_2CH_2OPOCl_2$	106–107/30 mm.	FCH_2CH_2OH to $POCl_3$	35		(66)
20.	$FCH_2COSCH_2CH_2Cl$	104–105/33 mm.	$FCH_2COCl + ClCH_2CH_2SH$	63	Less toxic; nonvesicant	(45, 94)
21.	$FCH_2CH_2OC_{10}H_7$	¶	$(FCH_2CH_2O)_2SO_2 + C_{10}H_7OH$	78	Much less toxic	(96)

* Pressures not indicated are atmospheric. †Melting point, 108°C. ‡Melting point, 64°C. §Melting point, 65°C. ¶Melting point, 50°C.

organic solvents. When it is distilled at atmospheric pressure it decomposes, giving hydrogen fluoride and butyrolactone (42).

E. OTHER "FLUOROACETATES"

Several other "fluoroacetates" were prepared and tested for their toxicity during World War II. The preparative procedures and properties of these compounds are listed in table 7. None of them showed special interest as chemical warfare agents.

Among these "fluoroacetates" the following are mentioned here, because they are related to known war gases:

(*a*) α-Fluoro-*N*-(2-chloroethyl)acetamide (I) and α-fluoro-*N*,*N*-bis(2-chloroethyl)acetamide (II):

$$\underset{\text{I}}{FCH_2CONHCH_2CH_2Cl} \qquad \underset{\text{II}}{FCH_2CON(CH_2CH_2Cl)_2}$$

These compounds contain the group —NCH_2CH_2Cl, which occurs in the "nitrogen mustards," previously described. The preparation of α-fluoro-*N*-(2-chloroethyl)acetamide involved the chlorination with thionyl chloride of α-fluoro-*N*-(2-hydroxyethyl)acetamide, obtained from the condensation of methyl fluoroacetate with 2-aminoethanol.

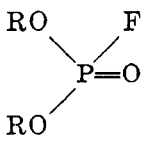
The α-fluoro-*N*,*N*-bis(2-chloroethyl)acetamide was prepared by following a similar procedure. Both compounds exhibit toxicities similar to that of methyl fluoroacetate, but do not have the expected vesicant properties (13).

(*b*) 2-Chloroethyl fluorothiolacetate, $FCH_2COSCH_2CH_2Cl$: The preparation of this fluorothiolacetate was attempted with the intention of obtaining a compound having the vesicant characteristics of "mustard gas" and the convulsant properties of the "fluoroacetates." It was obtained in 63 per cent yield by reacting fluoroacetyl chloride with 2-chloroethanethiol at 150°C. for 30 min. and then at 190°C. until no more hydrogen chloride was evolved. It is a colorless, unpleasant-smelling liquid. The toxicological tests show that this ester has no vesicant action and is less toxic than methyl fluoroacetate (45, 94).

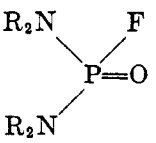
IV. FLUOPHOSPHATES

A. INTRODUCTION

This class comprises the diesters of fluophosphoric acid (I), the substituted diamidophosphoryl fluorides (II), and other related substances, such as the esters of alkylamido-substituted phosphoric acid (III) and the esters of alkanephosphonyl fluoride (IV)



I



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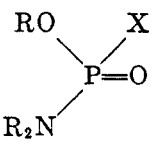

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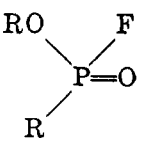

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in which R is an alkyl, aryl, or cycloalkyl group and X is a halogen, cyano, or cyanate substituent.

The discovery of compounds of this type was reported in 1932 by Lange and Krueger (70), who prepared dimethyl and diethyl fluophosphates. To this class belong the most toxic war gases developed during World War II, some of which were found interesting to the point of being manufactured on a large scale.

B. DIESTERS OF FLUOPHOSPHORIC ACID

The study of the diesters of fluophosphoric acid as chemical warfare agents started in England in 1940 (59). It is not reported when this study was begun in other countries; however, it was discovered at the end of World War II that the Germans also had tested a large number of these diesters.

One of the more thoroughly investigated compounds of this group was diisopropyl fluophosphate, known also as PF-3, which was prepared by the British and evaluated as a war gas especially in the United States. Over the last decade several analogs of this diester were prepared and tested, the most important of which are listed in table 8.

The diesters of fluophosphoric acid are highly toxic when inhaled, producing a quick knock-out action comparable to that of hydrogen cyanide. The toxicity of some of these fluophosphates is higher than that of phosgene. Their vapors have a pronounced effect on the eyes. Although there is no tear formation during the exposure, the pupils remain severely contracted for several days and vision is seriously affected, especially at night. These effects, in the case of the most toxic representatives of this group, can be produced by exposure to concentrations sufficiently low as to give no sensory warning. In addition, these compounds are the most powerful and specific enzyme inhibitors known. They inhibit the cholinesterase activity of human plasma and their action is progressive and irreversible (120).

From the data reported in tables 8, 9, and 10, it is possible to deduce some interesting correlations between chemical constitution and toxicity of the fluophosphates, $(RO)_2POF$ (R is alkyl):

(a) Diesters with branched chains are more effective than those with straight chains, and branching of the chain at the carbon atom adjacent to the oxygen appears to confer higher toxicity than branching at the end of the chain.

(b) Replacement of the fluorine atom by another substituent, such as chlorine, cyano, thiocyanate, or methylamino, markedly decreases the myotic effect and other toxic characteristics.

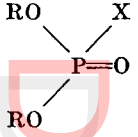
(c) Introduction of one or more methylene groups between the fluorine and the phosphorus atoms lowers the toxicity.

(d) Replacement of the oxygen by sulfur in the RO— groups also reduces the toxicity.

(e) Replacement of one or both RO— groups by a $(CH_3)_2N$— group progressively increases the toxicity. However, two $(CH_3)_2N$— groups nullify the myotic properties.

TABLE 8

Diesters of fluophosphoric acid and related compounds



NO.	R	X	BOILING POINT	REACTANTS	YIELD	TOXICITY COMPARED WITH DIISOPROPYL FLUOPHOSPHATE		REFERENCES
						L.C.$_{50}$ *	Myotic effect	
			°C.		*per cent*			
1.	CH_3	F	149/760 mm.	$Ag_2PO_3F + CH_3I$		Less toxic	Weaker	(70, 92, 108)
2.	C_2H_5	F	171/760 mm.	$(C_2H_5O)_2POCl + NaF$	90.3	Less toxic	Weaker	(18, 92, 108)
3.	*n*-C_3H_7	F	98–100/20 mm.	$POCl_2F + n\text{-}C_3H_7OH$	93	Less toxic	Weaker	(18)
4.	*i*-C_3H_7	F	183/760 mm.	$(i\text{-}C_3H_7O)_2POCl + NaF$	90	Standard		(92)
5.	*n*-C_4H_9	F	128/30 mm.	$Ag_2PO_3F + n\text{-}C_4H_9I$		Less toxic	Negligible	(24)
6.	*sec*-C_4H_9	F	62–64/0.8 mm.	$(sec\text{-}C_4H_9O)_2POCl + NaF$	68	Comparable	Comparable	(24, 73)
7.	$(CH_3)_2CHCH_2CH_2$	F	135–138/23 mm.	$[(CH_3)_2CHCH_2CH_2O]_2POCl + NaF$		Negligible	None	(24)
8.	$(CH_3)_2CHCH_2CH(CH_3)$	F	102–103/2.7 mm.	$[(CH_3)_2CHCH_2CH(CH_3)O]_2POCl +$ NaF		Comparable	Stronger	(24)
9.	C_2H_5	Cl	92/17 mm.	$(C_2H_5O)_2POH + Cl_2$	87	Negligible	None	(76, 95)
10.	C_2H_5	CN	90–91/11 mm.	$(C_2H_5O)_3P + CNI$	46	Negligible		(75, 95)
11.	C_2H_5	SCN	40/13 mm.	$(C_2H_5O)_2POCl + KSCN$		Negligible		(95)
12.	C_2H_5	$NHCH_3$	130/15 mm.	$(C_2H_5O)_2POCl + CH_3NH_2$	84	Negligible	None	(95)
13.	C_2H_5	CH_2CH_2F	74–75/11 mm.	$(C_2H_5O)_3P + BrCH_2CH_2F$	17	Negligible		(95)
14.	*sec*-C_4H_9	CH_2F	96–100/3 mm.	$(sec\text{-}C_4H_9O)_2POF + CH_2N_2$		Slightly toxic	Negligible	(95)
15.	FCH_2CH_2	F	125–127/13 mm.	$POCl_2F + HOCH_2CH_2F$	50	Less toxic		(18)
16.	$ClCH_2CH_2$	F	142–144/15 mm.	$POCl_2F + HOCH_2CH_2Cl$		Negligible		(18)
17.	C_6H_{11}	F	90–96/0.02 mm.	$POCl_2F + C_6H_{11}OH$	70	More toxic	Comparable	(18, 73)
18.	RO = C_2H_5S	F	104–107/15 mm.	$POCl_2F + C_2H_5SH$		Negligible	None	(18, 75)

* Concentration in milligrams per liter required to kill 50 per cent of the mice exposed for 10 min. L.C.$_{50}$ of diisopropyl fluophosphate = 0.44 mg./l. (92).

1. Methods of preparation

The original method for preparing these compounds is based upon the reaction of alkyl iodides with silver fluophosphate, as shown in the following steps:

$$P_2O_5 + 3NH_4F \rightarrow NH_4OPOF_2 + (NH_4O)_2POF$$

$$(NH_4O)_2POF + 2AgNO_3 \rightarrow (AgO)_2POF + 2NH_4NO_3$$

$$(AgO)_2POF + 2RI \rightarrow (RO)_2POF + 2AgI$$

This method is fairly involved and gives less than 10 per cent yields of dialkyl fluophosphates, based on ammonium fluoride (70). Subsequently it was found that the dialkyl fluophosphates could be easily prepared in 90 per cent yields by the action of sodium fluoride on the corresponding dialkyl chlorophosphates (77, 92, 102):

$$(RO)_2POCl + NaF \rightarrow (RO)_2POF + NaCl$$

However, for large-scale production this development was of little interest until a convenient way was found for preparing the dialkyl chlorophosphates. Prior to World War II, these compounds had been prepared by the following methods:

(*a*) Chlorination of a trialkyl phosphite, prepared by the reaction of phosphorus trichloride with the appropriate alcohol and pyridine:

$$PCl_3 + 3ROH + 3C_5H_5N \rightarrow (RO)_3P + 3C_5H_5N \cdot HCl$$

$$(RO)_3P + Cl_2 \rightarrow (RO)_2POCl + RCl$$

This method gives very good results on a laboratory scale, but it is not adaptable to industrial production, because of the large pyridine requirement (80, 121).

(*b*) Reaction of phosphoryl chloride with a trialkyl phosphate, obtained from the appropriate alcohol, phosphoryl chloride, and pyridine:

$$POCl_3 + 3ROH + 3C_5H_5N \rightarrow (RO)_3PO + 3C_5H_5N \cdot HCl$$

$$2(RO)_3PO + POCl_3 \rightarrow 3(RO)_2POCl$$

This route, besides requiring pyridine as in method (*a*), produces considerable quantities of alkyl dichlorophosphate, $ROPOCl_2$, as a by-product (32).

During World War II, in the attempt to dispense with pyridine, it was found that dialkyl phosphites could be obtained in 90 per cent yields by the action of phosphorus trichloride on the appropriate alcohol in the absence of a tertiary base (76):

$$PCl_3 + 3ROH \rightarrow (RO)_2POH + RCl + 2HCl$$

These dialkyl phosphites could then be converted, also in high yields, into the corresponding dialkyl chlorophosphates by treatment with chlorine (76):

$$(RO)_2POH + Cl_2 \rightarrow (RO)_2POCl + HCl$$

The process for manufacturing diisopropyl fluophosphate, developed as a result of this war-time investigation, consisted in adding phosphorus trichloride to a carbon tetrachloride solution of isopropyl alcohol without external cooling. The crude diisopropyl phosphite thus formed, still in carbon tetrachloride solution, was first treated with chlorine, while keeping the temperature at 0°C., then refluxed with sodium fluoride. The overall yield was 75 per cent, based on phosphorus trichloride (92). This method formed the basis of the procedure used in the United States for the manufacture of dimethyl and diisopropyl fluophosphates on a pilot-plant scale (51, 55, 61).

Since World War II, the following methods for preparing the dialkyl chlorophosphates have been developed:

(*a*) Treatment of a dialkyl phosphite with sulfuryl chloride at 35–40°C. By using this method diisopropyl and diethyl chlorophosphates were obtained in 83 and 90 per cent yields, respectively (4).

(*b*) Treatment of a dialkyl phosphite with an excess of carbon tetrachloride and 10–15 mole per cent of a tertiary base, at room temperature (3, 111):

$$(RO)_2POH + CCl_4 \xrightarrow{R_3N} (RO)_2POCl + CHCl_3$$

Yields as high as 85 per cent are reported (111). The main reaction is accompanied by a side reaction which yields a high-boiling product and the hydrochloride of the base. These products probably result from the reaction between the dialkyl phosphite and the dialkyl chlorophosphate in the presence of the base.

The diesters of fluophosphoric acid were prepared also by using the following methods:

(*a*) Condensation of fluophosphoryl chloride with the appropriate alcohol (18):

$$Cl_2POF + 2ROH \rightarrow (RO)_2POF + 2HCl$$

This reaction depends upon the marked difference in reactivity between the chlorine atoms and the fluorine atom of fluophosphoryl chloride. The yields are very good; however, this method is limited by the availability of fluophosphoryl chloride.

(*b*) Reaction of alkyl dichlorophosphates with sodium fluoride and an alcohol in the presence of an inert solvent (106):

$$C_2H_5OPOCl_2 + C_2H_5OH + 3NaF \rightarrow (C_2H_5O)_2POF + 2NaCl + NaHF_2$$

(*c*) Reaction of an alkyl- or a dialkyl-amidophosphoryl chloride with sodium fluoride and an alcohol in the presence of benzene (106):

$$Cl_2PON(CH_3)_2 + NaF + 2C_2H_5OH \rightarrow (C_2H_5O)_2POF + (CH_3)_2NH \cdot HCl + NaCl$$

2. Properties and reactions

The diesters of fluophosphoric acid are colorless liquids of very faint odor. Generally they have high boiling points and low volatilities (*cf.* table 8). They are hydrolyzed by water to yield two equivalents of acid:

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$$(RO)_2POF + H_2O \rightarrow (RO)_2\overset{\overset{OH}{|}}{P}{=}O + HF$$

The hydrolysis of the diisopropyl fluophosphate is fairly slow. In the presence of a large excess of water (1 per cent solution), 72 hr. are required to complete the hydrolysis at 15°C. Dimethyl and diethyl fluophosphates are hydrolyzed much more quickly (92). Acids and bases catalyze this hydrolysis (60). In alkaline solution diisopropyl fluophosphate hydrolyzes very rapidly. With equivalent concentrations corresponding to the following equation, the liberation of fluoride anion is complete in about 15 min. at 25°C. (119).

$$(C_3H_7O)_2POF + 2NaOH \rightarrow (C_3H_7O)_2POONa + NaF + H_2O$$

The dicyclohexyl fluophosphate is very stable and vigorous agitation with water at 20°C. does not produce any appreciable hydrolysis. Only after several hours of refluxing with water is it completely hydrolyzed. In the presence of 2 per cent sodium hydroxide solution and with occasional shaking at 20°C., the hydrolysis of this fluophosphate proceeds to an extent of only 64 per cent after 220 min. (18).

C. SUBSTITUTED DIAMIDOPHOSPHORYL FLUORIDES

The substituted diamidophosphoryl fluorides, $(R_2N)_2POF$ and $(RNH)_2POF$, known also as "nitrogen fluophosphonates," were taken into consideration by the Germans in 1940 (103) and by the English in 1942 (52).

These compounds are highly toxic when inhaled, but unlike the diesters of fluophosphoric acid, they do not show any myotic action and are relatively less effective as enzyme inhibitors. Among the various substances of this group investigated, the tetramethyldiamidophosphoryl fluoride is the most interesting, since it is four times as toxic as diisopropyl fluophosphate (52). The preparation and properties of this fluoride and its analogs have been widely studied. However, none of these compounds proved promising as a war gas. Some of the substituted diamidophosphoryl fluorides are claimed to be useful insecticides, bactericides, and fungicides (75, 103).

1. Methods of preparation

A convenient method for preparing these compounds is based upon the reaction of the substituted diamidophosphoryl chlorides with sodium fluoride in an organic solvent such as benzene (105, 107):

$$(R_2N)_2POCl + NaF \rightarrow (R_2N)_2POF + NaCl$$

The substituted diamidophosphoryl chlorides required for the above reaction were obtained in high yields by condensing the appropriate amine with the calculated amount of phosphoryl chloride in cold ethereal solution (23, 78):

$$Cl_2POCl + 4R_2NH \rightarrow (R_2N)_2POCl + 2R_2NH \cdot HCl$$

The fluorination step can also be effected by other fluorinating agents, such as potassium fluoride or zinc fluoride (23, 107).

Another general method of preparation involves the reaction of fluophosphoryl chloride with a primary or secondary amine in benzene or ether solution (52, 75):

$$Cl_2POF + 4RNH_2 \rightarrow (RNH)_2POF + 2RNH_2 \cdot HCl$$

The yields of this reaction are fairly good, varying from 45 per cent to 95 per cent, but this method is limited by the availability of fluophosphoryl chloride. In table 9 are listed several substituted diamidophosphoryl fluorides which were obtained by applying this procedure.

TABLE 9

N,N'-Substituted diamidophosphoryl fluorides, X_2POF, prepared by reacting fluophosphoryl chloride with the corresponding amines (52)

NO.	X	BOILING POINT	MELTING POINT	YIELD	TOXICITY* L.D.$_{50}$
		°C.	°C.	*per cent*	*mg./kg.*
1.....	$(CH_3)_2N$	86/15 mm.		67	1
2.....	$(C_2H_5)_2N$	124–125/20 mm.			160
3.....	C_4H_9NH		59.5		16
4.....	C_6H_5NH		145		90
5.....	$C_6H_5NCH_3$	163–165/0.08 mm.		60	160
6.....	$C_6H_5CH_2NH$		96	66	10
7.....	$C_5H_{10}N$	145/0.3 mm.		43	320
8.....	$C_6H_{11}NH$		127	95	9

* Dose in milligrams per kilogram of body weight required to kill 50 per cent of the mice treated by subcutaneous injection.

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For the specific preparation of tetramethyldiamidophosphoryl fluoride the following methods were also used:

(*a*) Condensation of dimethylamidophosphoryl fluoride with dimethylamine (104):

$$(CH_3)_2NPOF_2 + 2(CH_3)_2NH \rightarrow [(CH_3)_2N]_2POF + (CH_3)_2NH \cdot HF$$

(*b*) Condensation of phosphoryl fluoride with dimethylamine (16):

$$POF_3 + 4(CH_3)_2NH \rightarrow [(CH_3)_2N]_2POF + 2(CH_3)_2NH \cdot HF$$

Both of these methods are uneconomical, owing to the loss of fluorine involved in the reaction.

2. Properties and reactions

The substituted diamidophosphoryl fluorides are either colorless liquids of fairly high boiling points or crystalline substances (*cf.* table 9). The low-molecular-weight members of this group are soluble in water, giving almost neutral solutions, which do not undergo any detectable change for a long time. The tetramethyldiamidophosphoryl fluoride is not affected by contact with water at 18°C. for 6 hr. (52). These fluorides are slowly hydrolyzed by dilute sodium hydroxide solution at room temperature. The extent of this hydrolysis at 15°C. in the case of tetramethyldiamidophosphoryl fluoride is about 9 per cent after

30 min. and about 30 per cent after 500 hr. Refluxed with sodium hydroxide, tetramethyldiamidophosphoryl fluoride is completely hydrolyzed in 30 min., according to the equation (52):

$$[(CH_3)_2N]_2POF + 2NaOH \rightarrow [(CH_3)_2N]_2POONa + H_2O + NaF$$

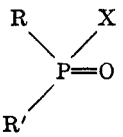
The *N*,*N*′-diphenyldiamidophosphoryl fluoride is even more resistant to hydrolysis; it can be crystallized from aqueous alcohol.

D. OTHER PHOSPHORUS COMPOUNDS

Among the various phosphorus compounds related to the diesters of fluophosphoric acid, which received special attention as war gases, are the esters of

TABLE 10

Various phosphorus compounds



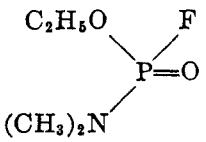
NO.	R	R′	X	BOILING POINT	TOXICITY		REFERENCES
					Compared with diisopropyl fluophosphate*	$L.D._{50}$	
				°C		*mg./kg.*	
1 ...	C_2H_5O	$(CH_3)_2N$	F	76–78/18 mm.		2.5	(23)
2 ...	C_2H_5O	$(CH_3)_2N$	CN		Five times as toxic		(40)
3 ...	C_2H_5O	C_6H_5NH	F	100–150/0.2 mm.†		10	(23)
4 ...	CH_3	$(CH_3)_2CHO$	F		Twenty times as toxic		(40)

* $L.D._{50}$ of diisopropyl fluophosphate by subcutaneous injection into mice = 4 mg./kg. (92).

† Melting point, 50°C.

dimethylamidofluo- and dimethylamidocyanophosphoric acid and the esters of methanephosphonyl fluoride (*cf.* table 10). The toxic properties of these substances are similar to those of the dialkyl fluophosphates (23, 40). The ethyl ester of dimethylamidocyanophosphoric acid was manufactured on a large scale in Germany and at the end of hostilities a total of 12,000 metric tons was captured (116). This amount, when compared with the 25,000 metric tons of "mustard gas" produced by the Germans during World War II, indicates the importance attributed by them to this new agent.

1. Ethyl ester of dimethylamidofluophosphoric acid



This ester was prepared in England in 1943 with the hope of obtaining a compound having the myotic effect of the dialkyl fluophosphates and the high toxicity of the substituted diamidophosphoryl fluorides (23). The synthesis was carried out by the following steps:

(*a*) Reaction of phosphoryl chloride with ethyl alcohol in cold ether (95):

$$Cl_2POCl + C_2H_5OH \rightarrow C_2H_5OPOCl_2 + HCl$$

(83 per cent yield)

(*b*) Condensation of the ethyl dichlorophosphate with dimethylamine, also in cold ether (23):

$$C_2H_5OPOCl_2 + 2(CH_3)_2NH \rightarrow \begin{matrix} C_2H_5O & & Cl \\ & \diagdown \quad \diagup & \\ & P{=}O & \\ & \diagup \quad \diagdown & \\ (CH_3)_2N & & \end{matrix} + (CH_3)_2NH\cdot HCl$$

(62 per cent yield)

(*c*) Reaction of the ethyl ester of dimethylamidochlorophosphoric acid with potassium fluoride in carbon tetrachloride or toluene (23):

$$\begin{matrix} C_2H_5O & & Cl \\ & \diagdown \quad \diagup & \\ & P{=}O & \\ & \diagup \quad \diagdown & \\ (CH_3)_2N & & \end{matrix} + KF \rightarrow \begin{matrix} C_2H_5O & & F \\ & \diagdown \quad \diagup & \\ & P{=}O & \\ & \diagup \quad \diagdown & \\ (CH_3)_2N & & \end{matrix} + KCl$$

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The ethyl ester of dimethylamidofluophosphoric acid is about twice as toxic as diisopropyl fluophosphate and, as expected, exhibits myotic properties.

An analogous compound, the ethyl ester of phenylamidofluophosphoric acid, was prepared by adding one mole of fluophosphoryl chloride to one mole of ethyl alcohol and treating the resulting ethyl chlorofluophosphate with aniline (23):

$$Cl_2POF \xrightarrow{C_2H_5OH} \begin{matrix} C_2H_5O \\ | \\ ClPOF \end{matrix} \xrightarrow{C_6H_5NH_2} \begin{matrix} C_2H_5O \\ | \\ C_6H_5NHPOF \end{matrix}$$

This compound is less toxic than the ester described above.

2. Ethyl ester of dimethylamidocyanophosphoric acid

$$\begin{matrix} C_2H_5O & & CN \\ & \diagdown \quad \diagup & \\ & P{=}O & \\ & \diagup \quad \diagdown & \\ (CH_3)_2N & & \end{matrix}$$

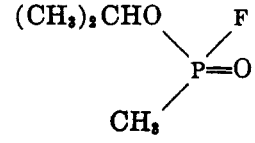
This ester is known also as Tabun or Trilon 83. Phosphoryl chloride was used for its preparation, according to the following scheme (40, 116):

$$POCl_3 \xrightarrow{(CH_3)_2NH} (CH_3)_2NPOCl_2 \xrightarrow{NaCN + C_2H_5OH} \begin{matrix} C_2H_5O \\ | \\ (CH_3)_2NPOCN \end{matrix}$$

An industrial plant for the production of 1000 metric tons per month was operating in Germany at the end of World War II (115).

This ester is a colorless liquid of low volatility. Like the dialkyl fluophosphates, it is easily hydrolyzed by caustic and reacts slowly with water. It is five times as toxic as diisopropyl fluophosphate. Its toxic effects are produced either by inhalation or by absorption through the skin. The Germans intended to use it as an aerosol, by dispersing it from shells or bombs loaded with explosive (40).

3. Isopropyl ester of methanephosphonyl fluoride



This ester, known also as Sarin or Trilon 46, is a colorless liquid of boiling point lower than that of the ethyl dimethylamidocyanophosphate. It is reported to be twenty times as toxic as diisopropyl fluophosphate. At the end of World War II, two plants were under construction in Germany for a total production of 600 metric tons per month (40, 115).

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